



JC07 Rec'd PCT/PTO 19 MAR 2002

10/088400

TRANSMITTAL LETTER TO THE UNITED STATES

ATTORNEY'S DOCKET NUMBER 0480/01219

DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/09149	19 September 2000	24 September 1999

TITLE OF INVENTION: RATE-CONTROLLED PARTICLES

APPLICANT(S) FOR DO/EO/US Thomas HANTKE, Bettina REHBOCK, Joerg ROSENBERG, Joerg BREITENBACH

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
  2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
  3. /X/ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
  4. /x/ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
  5. /X/ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
    - a./X/ is transmitted herewith (required only if not transmitted by the International Bureau).
    - b./ / has been transmitted by the International Bureau.
    - c./ / is not required, as the application was filed in the United States Receiving Office (RO/USO).
  6. /X/ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
  7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
    - a./ / are transmitted herewith (required only if not transmitted by the International Bureau).
    - b./ / have been transmitted by the International Bureau.
    - c./ / have not been made; however, the time limit for making such amendments has NOT expired.
    - d./ / have not been made and will not be made.
  8. / / A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
  9. / / An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
  10. / / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
- Items 11. to 16. below concern other document(s) or information included:
11. / / An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
  12. / / An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
  13. /X/ A FIRST preliminary amendment.  
/ / A SECOND or SUBSEQUENT preliminary amendment.
  14. / / A substitute specification.
  15. / / A change of power of attorney and/or address letter.
  16. /x/ Other items or information.  
International Search Report  
International Preliminary Examination Report

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0480/01219

a./X/ A check in the amount of \$890.- to cover the above fees is enclosed.

b./ / Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees. A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **11-0345**. A duplicate copy of this sheet is enclosed.

**SEND ALL CORRESPONDENCE TO:**  
**KEIL & WEINKAUF**  
1101 Connecticut Ave., N.W.  
Washington, D. C. 20036

Registration No. 18,967

10/088400  
JC10 Rec'd PCT/PTO 19 MAR 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of )  
HANTKE et al. ) BOX PCT  
)  
International Application )  
PCT/EP 00/09149 )  
)  
Filed: September 19, 2000 )  
)

For: RATE-CONTROLLED PARTICLES

PRELIMINARY AMENDMENT

Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-identified application as follows:

IN THE CLAIMS

Kindly amend the claims as shown on the attached sheets.

R E M A R K S

The claims have been amended to eliminate multiple dependency and to place them in better form for U.S. filing. No new matter is included.

A clean copy of the claims is attached.

Favorable action is solicited.

Respectfully submitted,

KEIL & WEINKAUF



Herbert B. Keil  
Reg. No. 18,967

1101 Connecticut Ave., N.W.  
Washington, D.C. 20036

(202)659-0100



4-[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-

pyrimidinyl]amino]benzonitrile;

4-[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-

amino]benzonitrile;

4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-

pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-

pyrimidinyl]amino]benzonitrile;

4-[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]-amino]benzonitrile;

4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-

yl]amino]benzonitrile;

4-[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-

yl]amino]benzonitrile;

1[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;

(-)-[2S-[2alpha, 4alpha(S\*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[[(4-methyl-

CLEAN VERSION OF AMENDED CLAIMS - 0480/01219

4H-1,2,4-triazol-3-yl)thio)methyl]-1,3-dioxolan-4-yl]methoxyl]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one,

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

14. Pharmaceutical dosage form, comprising particles according to a claim 1.



MARKED VERSION OF AMENDED CLAIMS - 0480/01219

amino]benzonitrile;

4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile;

4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile;

4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;

1[4-[4-[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;

(-)-[2S-[2alpha, 4alpha(S\*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[(4-methyl-





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Het; or

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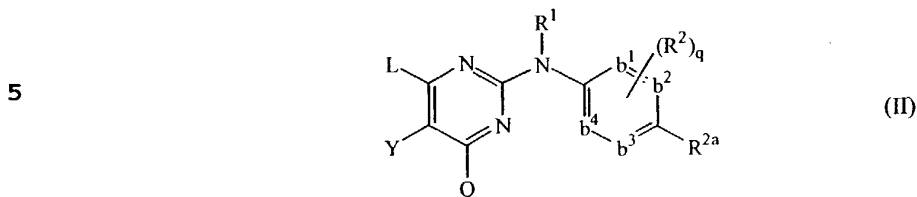
R<sup>6</sup> and R<sup>7</sup> each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy,

**10**

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or a compound of formula



10 the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$  represents a bivalent radical of formula

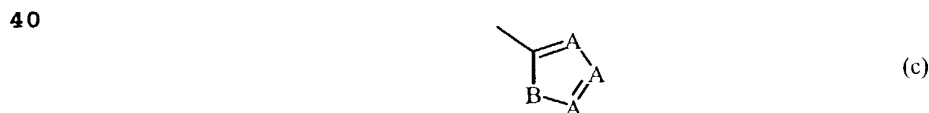
- 15
- $-CH=CH-C(R^{2a})=CH-CH=$  (b-1);
  - $-N=CH-C(R^{2a})=CH-CH=$  (b-2);
  - $-CH=N-C(R^{2a})=CH-CH=$  (b-3);
  - $-N=CH-C(R^{2a})=N-CH=$  (b-4);
  - $-N=CH-C(R^{2a})=CH-N=$  (b-5);
  - $-CH=N-C(R^{2a})=N-CH=$  (b-6);
  - 20  $-N=N-C(R^{2a})=CH-CH=$  (b-7);

*q* is 0, 1, 2; or where possible *q* is 3 or 4;

*R*<sup>1</sup> is hydrogen, aryl, formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxycarbonyl, C<sub>1-6</sub>alkyl substituted with formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxycarbonyl;

25 *R*<sup>2a</sup> is cyano, aminocarbonyl, mono- or di(methyl)amino-carbonyl, C<sub>1-6</sub>alkyl substituted with cyano, amino-carbonyl or mono- or di(methyl)aminocarbonyl, C<sub>2-6</sub>alkenyl substituted with cyano, or C<sub>2-6</sub>alkynyl substituted with cyano;

30 each *R*<sup>2</sup> independently is hydroxy, halo, C<sub>1-6</sub>alkyl optionally substituted with cyano or  $-C(=O)R^6$ , C<sub>3-7</sub>cycloalkyl, C<sub>2-6</sub>alkenyl optionally substituted with one or more halogen atoms or cyano, C<sub>2-6</sub>alkynyl optionally substituted with one or more halogen atoms or cyano, C<sub>1-6</sub>alkyloxy, C<sub>1-6</sub>alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C<sub>1-6</sub>alkyl)amino, polyhalomethyl, polyhalomethyloxy, 35 polyhalomethylthio,  $-S(=O)_pR^6$ ,  $-NH-S(=O)_pR^6$ ,  $-C(=O)R^6$ ,  $-NHC(=O)H$ ,  $-C(=O)NHNH_2$ ,  $-NHC(=O)R^6$ ,  $-C(=NH)R^6$  or a radical of formula



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R<sup>6</sup> is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>2-10</sub>alkynyl, C<sub>3-7</sub>cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

\* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C<sub>1-6</sub>alkyl-carbonyl,

\* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R<sup>2</sup>; or

R<sup>3</sup> is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R<sup>2</sup>; and

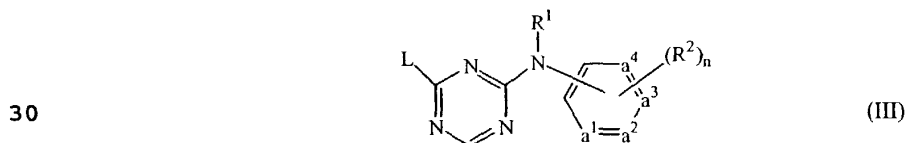
X is  $\text{-NR}^1\text{-}$ ,  $\text{-NH-NH-}$ ,  $\text{-N=N-}$ ,  $\text{-O-}$ ,  $\text{-C(=O)-}$ ,  $\text{-CHOH-}$ ,  $\text{-S-}$ ,  $\text{-S(=O)-}$  or  $\text{-S(=O)}_2\text{-}$ ;

Q represents hydrogen, C<sub>1-6</sub>alkyl, halo, polyhaloC<sub>1-6</sub>alkyl or -NR<sup>4</sup>R<sup>5</sup>; and

R<sup>4</sup> and R<sup>5</sup> are each independently selected from hydrogen, hydroxy, C<sub>1-12</sub>alkyl, C<sub>1-12</sub>alkyloxy, C<sub>1-12</sub>alkylcarbonyl, C<sub>1-12</sub>alkyloxycarbonyl, aryl, amino, mono- or di(C<sub>1-12</sub>alkyl)amino, mono- or di(C<sub>1-12</sub>alkyl)aminocarbonyl wherein each of the aforementioned C<sub>1-12</sub>alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C<sub>1-6</sub>alkyloxy, hydroxyC<sub>1-6</sub>alkyloxy, carboxyl, C<sub>1-6</sub>alkyloxycarbonyl, cyano, amino, imino, mono- or di(C<sub>1-6</sub>alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)<sub>p</sub>R<sup>6</sup>, -NH-S(=O)<sub>p</sub>R<sup>6</sup>, -C(=O)R<sup>6</sup>, -NHC(=O)H, -C(=O)NHNH<sub>2</sub>, -NHC(=O)R<sup>6</sup>, -C(=NH)R<sup>6</sup>, aryl and Het: or

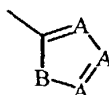
R<sup>4</sup> and R<sup>5</sup> taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C<sub>1-12</sub>alkyl)aminoC<sub>1-4</sub>-alkylidene;

- Y represents hydroxy, halo, C<sub>3-7</sub>cycloalkyl, C<sub>2-6</sub>alkenyl optionally substituted with one or more halogen atoms, C<sub>2-6</sub>alkynyl optionally substituted with one or more halogen atoms, C<sub>1-6</sub>alkyl substituted with cyano or
- 5 -C(=O)R<sup>6</sup>, C<sub>1-6</sub>alkyloxy, C<sub>1-6</sub>alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C<sub>1-6</sub>alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)<sub>p</sub>R<sup>6</sup>, -NH-S(=O)<sub>p</sub>R<sup>6</sup>, -C(=O)R<sup>6</sup>, -NHC(=O)H, -C(=O)NHNH<sub>2</sub>, -NHC(=O)R<sup>6</sup>, -C(=NH)R<sup>6</sup> or aryl;
- 10 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>1-6</sub>alkyloxy, cyano, nitro, polyhaloC<sub>1-6</sub>alkyl and polyhaloC<sub>1-6</sub>alkyloxy;
- Het is an aliphatic or aromatic heterocyclic radical;
- 15 said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said
- 20 aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,
- 25 or a compound of formula



- a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof,
- 35 wherein
- a<sup>1</sup>=a<sup>2</sup>-a<sup>3</sup>=a<sup>4</sup>- represents a bivalent radical of formula
- CH=CH-CH=CH- (a-1);
- N=CH-CH=CH- (a-2);
- N=CH-N=CH- (a-3);
- 40 -N=CH-CH=N- (a-4);
- N=N-CH=CH- (a-5);
- n is 0, 1, 2, 3 or 4; and in case -a<sup>1</sup>=a<sup>2</sup>-a<sup>3</sup>=a<sup>4</sup>- is (a-1), then n may also be 5;
- R<sup>1</sup> is hydrogen, aryl, formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl,
- 45 C<sub>1-6</sub>alkyloxycarbonyl, C<sub>1-6</sub>alkyl substituted with formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxycarbonyl; and

each  $R^2$  independently is hydroxy, halo,  $C_{1-6}$ alkyl optionally substituted with cyano or  $-C(=O)R^4$ ,  $C_{3-7}$ cycloalkyl,  $C_{2-6}$ alkenyl optionally substituted with one or more halogen atoms or cyano,  $C_{2-6}$ alkynyl optionally substituted with one or more halogen atoms or cyano,  $C_{1-6}$ alkyloxy,  $C_{1-6}$ alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di( $C_{1-6}$ alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio,  $-S(=O)_pR^4$ ,  $-NH-S(=O)_pR^4$ ,  $-C(=O)R^4$ ,  $-NHC(=O)H$ ,  $-C(=O)NHNH_2$ ,  $-NHC(=O)R^4$ ,  $-C(=NH)R^4$  or a radical of formula



(c)

wherein each A independently is N, CH or  $CR^4$ ;  
 B is NH, O, S or  $NR^4$ ;  
 p is 1 or 2; and  
 $R^4$  is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is  $C_{4-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{2-10}$ alkynyl,  $C_{3-7}$ cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

- \*  $C_{3-7}$ cycloalkyl,
- \* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo,  $C_{1-6}$ alkyl, hydroxy,  $C_{1-6}$ alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and  $C_{1-6}$ alkyl-carbonyl,
- \* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in  $R^2$ ; or

L is  $-X-R^3$  wherein

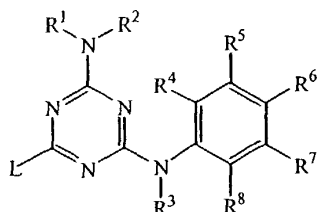
$R^3$  is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with two, three, four or five substituents each independently selected from the substituents defined in  $R^2$ ; and

X is  $-NR^1-$ ,  $-NH-NH-$ ,  $-N=N-$ ,  $-O-$ ,  $-C(=O)-$ ,  $-CHOH-$ ,  $-S-$ ,  $-S(=O)-$  or  $-S(=O)_2-$ ;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{1-6}$ alkyloxy, cyano, nitro, polyhalo $C_{1-6}$ alkyl and polyhalo $C_{1-6}$ alkyloxy,

or a compound of formula

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(IV)

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the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen; hydroxy; amino; C<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkylcarbonyl; C<sub>1-6</sub>alkyloxycarbonyl; Ar<sup>1</sup>; mono- or di(C<sub>1-6</sub>alkyl)amino; mono- or di(C<sub>1-6</sub>alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C<sub>1-6</sub>alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonylamino, hydroxy, hydroxyC<sub>1-6</sub>alkyloxy, carboxyl, mono- or di(C<sub>1-6</sub>alkyl)amino, C<sub>1-6</sub>alkyloxycarbonyl and thienyl; or

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R<sup>1</sup> and R<sup>2</sup> taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C<sub>1-6</sub>alkyl)aminoC<sub>1-4</sub>-alkylidene;

25

R<sup>3</sup> is hydrogen, Ar<sup>1</sup>, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxycarbonyl, C<sub>1-6</sub>alkyl substituted with C<sub>1-6</sub>alkyloxycarbonyl; and

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R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently selected from hydrogen, hydroxy, halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

L is C<sub>1-10</sub>alkyl; C<sub>3-10</sub>alkenyl; C<sub>3-10</sub>alkynyl; C<sub>3-7</sub>cycloalkyl; or

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L is C<sub>1-10</sub>alkyl substituted with one or two substituents independently selected from C<sub>3-7</sub>cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C<sub>1-6</sub>alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C<sub>1-6</sub>alkylcarbonyl; and,

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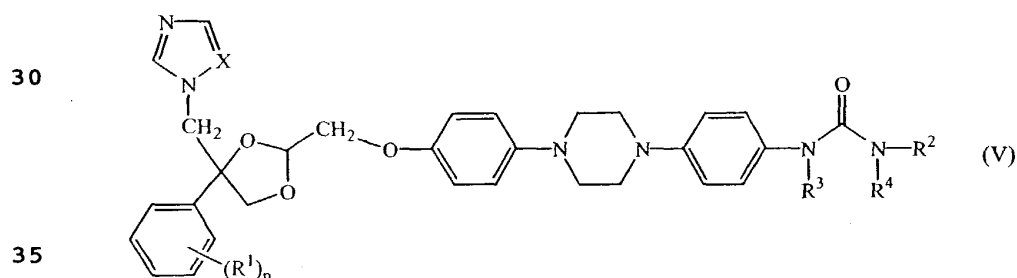


Ar<sup>1</sup> is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

Co. No.	Alk	R <sup>1</sup> /R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	R <sup>7</sup>	R <sup>8</sup>
a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH <sub>3</sub>	H	H	H	H
b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO <sub>2</sub>	H	H
c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H
d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO <sub>2</sub>	H	CH <sub>3</sub>	H	H
e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH <sub>2</sub>	H	H
f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF <sub>3</sub>	H	H	H
g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
n	Phenylmethyl	H/H	H	CH <sub>3</sub>	H	H	H	H
o	Phenylmethyl	H/H	H	H	H	H	H	H

are not included,

or a compound of formula



the N-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

n is zero, 1, 2 or 3;

X is N or CH;

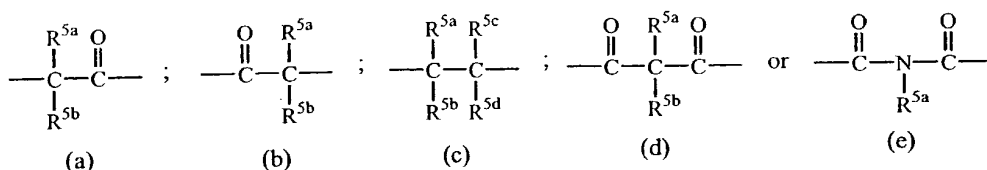
each R<sup>1</sup> independently is halo, nitro, cyano, amino, hydroxy, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxy or trifluoromethyl;

R<sup>2</sup> is hydrogen; C<sub>3-7</sub>alkenyl; C<sub>3-7</sub>alkynyl, aryl; C<sub>3-7</sub>cycloalkyl; C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl substituted with hydroxy, C<sub>1-4</sub>alkyloxy, C<sub>3-7</sub>cycloalkyl or aryl;

$R^3$  and  $R^4$  each independently are hydrogen,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl or aryl; or  
 $R^3$  and  $R^4$  taken together form a bivalent radical  $-R^3-R^4-$  of formula:

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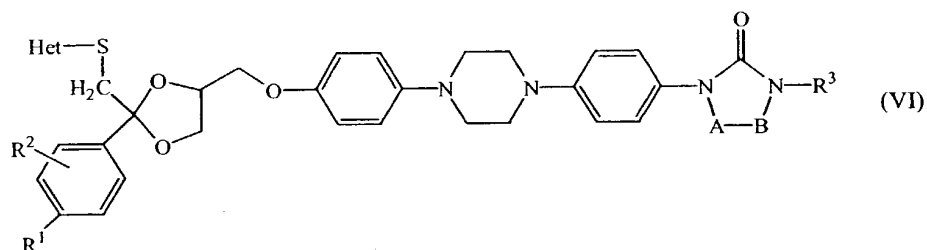


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wherein  $R^{5a}$ ,  $R^{5b}$ ,  $R^{5c}$ ,  $R^{5d}$  each independently are hydrogen,  $C_{1-6}$ alkyl or aryl; and  
 aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkyloxy or trifluoromethyl,  
 or a compound of formula

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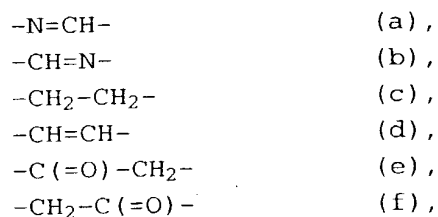
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the  $N$ -oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :

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in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by  $C_{1-6}$ alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by  $C_{1-6}$ alkyl;

45

$R^1$  is hydrogen,  $C_{1-6}$ alkyl or halo;  
 $R^2$  is hydrogen or halo;  
 $R^3$  is hydrogen;  $C_{1-8}$ alkyl;  $C_{3-6}$ cycloalkyl; or  $C_{1-8}$ alkyl substituted with hydroxy, oxo,  $C_{3-6}$ cycloalkyl or aryl;

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- 11



amino]benzonitrile;

4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-

pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-

pyrimidinyl]amino]benzonitrile;

4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]-amino]benzonitrile;

4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile;

4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-

yl]amino]benzonitrile;

1[4-[4-[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-

yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;

(-)-[2S-[2alpha, 4alpha(S\*)]]-4-[4-[4-[2-(4-chlorophenyl)-2-[(4-methyl-4H-

1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxyl]phenyl]-1-

piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one,

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically

isomeric form thereof.

14. Pharmaceutical dosage form, comprising particles according to a claim 1.
15. Pharmaceutical dosage forms according to claim 13, further comprising one or more pharmaceutically acceptable excipients.

JC10 Rec'd PCT/PTO 19 MAR 2002

Rate-controlled particles

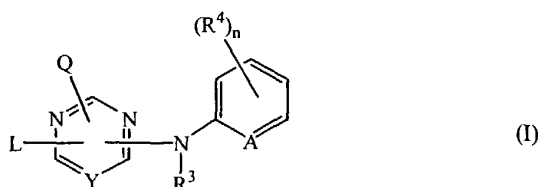
Specification

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The present invention concerns pharmaceutical compositions in the form of rate-controlled particles, comprising compounds of the formula (I) to (VI)

10 (I) is an antiviral compound of formula

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a N-oxide, a pharmaceutically acceptable addition salt or a  
20 stereochemically isomeric form thereof, wherein

Y is CR<sup>5</sup> or N;

A is CH, CR<sup>4</sup> or N;

n is 0, 1, 2, 3 or 4;

25 Q is -NR<sup>1</sup>R<sup>2</sup> or when Y is CR<sup>5</sup> then Q may also be hydrogen;

R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen, hydroxy, C<sub>1-12</sub>alkyl, C<sub>1-12</sub>alkyloxy, C<sub>1-12</sub>alkylcarbonyl, C<sub>1-12</sub>alkyloxycarbonyl, aryl, amino, mono- or di(C<sub>1-12</sub>alkyl)-amino, mono- or di(C<sub>1-12</sub>alkyl)aminocarbonyl wherein each of  
30 the aforementioned C<sub>1-12</sub>alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C<sub>1-6</sub>alkyloxy, hydroxy-C<sub>1-6</sub>alkyloxy, carboxyl, C<sub>1-6</sub>alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or

35 di(C<sub>1-6</sub>alkyl)amino, aryl and Het; or

R<sup>1</sup> and R<sup>2</sup> taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C<sub>1-12</sub>alkyl)aminoC<sub>1-4</sub>-alkylidene;

R<sup>3</sup> is hydrogen, aryl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy-carbonyl, C<sub>1-6</sub>alkyl substituted with C<sub>1-6</sub>alkyloxycarbonyl; and  
40 each R<sup>4</sup> independently is hydroxy, halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalo-methyloxy, or when Y is CR<sup>5</sup> then R<sup>4</sup> may also represent C<sub>1-6</sub>alkyl substituted with cyano or aminocarbonyl;

45 R<sup>5</sup> is hydrogen or C<sub>1-4</sub>alkyl;

L is -X<sup>1</sup>-R<sup>6</sup> or -X<sup>2</sup>-Alk-R<sup>7</sup> wherein

## 2

- R<sup>6</sup> and R<sup>7</sup> each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR<sup>5</sup> then R<sup>6</sup> and R<sup>7</sup> may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy and trihalomethyl; or when Y is N then R<sup>6</sup> and R<sup>7</sup> may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl;
- X<sup>1</sup> and X<sup>2</sup> are each independently -NR<sup>3</sup>-, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or -S(=O)<sub>2</sub>-;
- Alk is C<sub>1-4</sub>alkanediyl; or
- when Y is CR<sup>5</sup> then L may also be selected from C<sub>1-10</sub>alkyl, C<sub>3-10</sub>alkenyl, C<sub>3-10</sub>alkynyl, C<sub>3-7</sub>cycloalkyl, or C<sub>1-10</sub>alkyl substituted with one or two substituents independently selected from C<sub>3-7</sub>cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, C<sub>1-6</sub>alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and C<sub>1-6</sub>alkylcarbonyl;
- aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, nitro and trifluoromethyl;
- Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

The compounds of formula (I) can be prepared according to the methods described in the patent applications with application number PCT/EP99/02043 and PCT/EP99/02044.

(II) is an antiviral compound of formula



$-b^1=b^2-C(R^{2a})=b^3-b^4=$  represents a bivalent radical of formula

**15**  $-N=CH-C(R^{2a})=CH-CH=$  (b-2);

$$-\text{CH}=\text{N}-\text{C}(\text{R}^{2\text{a}})=\text{CH}-\text{CH}= \quad (\text{b-3}) ;$$
$$-\text{N}=\text{CH}-\text{C}(\text{R}^{2\text{a}})=\text{N}-\text{CH}= \quad (\text{b-4}) ;$$
$$-\text{N}=\text{CH}-\text{C}(\text{R}^{2\text{a}})=\text{CH}-\text{N}= \quad (\text{b-5}) ;$$
$$-\text{CH}=\text{N}-\text{C}(\text{R}^{2\text{a}})=\text{N}-\text{CH}= \quad (\text{b-6}) ;$$

20  $-N=N-C(R^{2a})=CH-CH=$  (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

R<sup>1</sup> is hydrogen, aryl, formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxycarbonyl, C<sub>1-6</sub>alkyl substituted with formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxycarbonyl;

25 R<sup>2a</sup> is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C<sub>1-6</sub>alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C<sub>2-6</sub>alkenyl substituted with cyano, or C<sub>2-6</sub>alkynyl substituted with cyano;

each R<sup>2</sup> independently is hydroxy, halo, C<sub>1-6</sub>alkyl optionally substituted with cyano or -C(=O)R<sup>6</sup>, C<sub>3-7</sub>cycloalkyl, C<sub>2-6</sub>alkenyl optionally substituted with one or more halogen atoms or cyano, C<sub>2-6</sub>alkynyl optionally substituted with one or more halogen atoms or cyano, C<sub>1-6</sub>alkyloxy, C<sub>1-6</sub>alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C<sub>1-6</sub>alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)<sub>p</sub>R<sup>6</sup>, -NH-S(=O)<sub>p</sub>R<sup>6</sup>, -C(=O)R<sup>6</sup>, -NHC(=O)H, -C(=O)NHNH<sub>2</sub>, -NHC(=O)R<sup>6</sup>, -C(=NH)R<sup>6</sup> or a radical of formula



wherein each A independently is N, CH or CR<sup>6</sup>;

B is NH, O, S or NR<sup>6</sup>;

45 p is 1 or 2; and

R<sup>6</sup> is methyl, amino, mono- or dimethylamino or polyhalomethyl;



L is C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>2-10</sub>alkynyl, C<sub>3-7</sub>cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

\* C<sub>3-7</sub>cycloalkyl,

5 \* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C<sub>1-6</sub>alkylcarbonyl,

10 \* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R<sup>2</sup>; or

15 L is -X-R<sup>3</sup> wherein

R<sup>3</sup> is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R<sup>2</sup>; and

20 X is -NR<sup>1</sup>-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)<sub>2</sub>-;

Q represents hydrogen, C<sub>1-6</sub>alkyl, halo, polyhaloC<sub>1-6</sub>alkyl or -NR<sup>4</sup>R<sup>5</sup>; and

25 R<sup>4</sup> and R<sup>5</sup> are each independently selected from hydrogen, hydroxy, C<sub>1-12</sub>alkyl, C<sub>1-12</sub>alkyloxy, C<sub>1-12</sub>alkylcarbonyl, C<sub>1-12</sub>alkyloxy-carbonyl, aryl, amino, mono- or di(C<sub>1-12</sub>alkyl)amino, mono- or di(C<sub>1-12</sub>alkyl)aminocarbonyl wherein each of the aforementioned C<sub>1-12</sub>alkyl groups may optionally and each individually be

30 substituted with one or two substituents each independently selected from hydroxy, C<sub>1-6</sub>alkyloxy, hydroxyC<sub>1-6</sub>alkyloxy, carboxyl, C<sub>1-6</sub>alkyloxy-carbonyl, cyano, amino, imino, mono- or di(C<sub>1-6</sub>alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)<sub>p</sub>R<sup>6</sup>, -NH-S(=O)<sub>p</sub>R<sup>6</sup>, -C(=O)R<sup>6</sup>, -NHC(=O)H, -C(=O)NHNH<sub>2</sub>, -NHC(=O)R<sup>6</sup>, -C(=NH)R<sup>6</sup>, aryl and Het; or

35 R<sup>4</sup> and R<sup>5</sup> taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C<sub>1-12</sub>alkyl)aminoC<sub>1-4</sub>alkylidene;

Y represents hydroxy, halo, C<sub>3-7</sub>cycloalkyl, C<sub>2-6</sub>alkenyl optionally substituted with one or more halogen atoms, C<sub>2-6</sub>alkynyl

40 optionally substituted with one or more halogen atoms, C<sub>1-6</sub>alkyl substituted with cyano or -C(=O)R<sup>6</sup>, C<sub>1-6</sub>alkyloxy, C<sub>1-6</sub>alkyloxy-carbonyl, carboxyl, cyano, nitro, amino, mono- or di(C<sub>1-6</sub>alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)<sub>p</sub>R<sup>6</sup>, -NH-S(=O)<sub>p</sub>R<sup>6</sup>, -C(=O)R<sup>6</sup>, -NHC(=O)H, -C(=O)NHNH<sub>2</sub>, -NHC(=O)R<sup>6</sup>, -C(=NH)R<sup>6</sup> or aryl;

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## 5

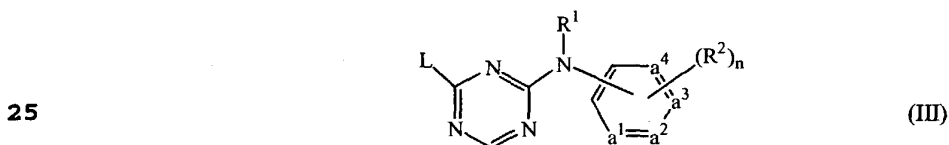
aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>1-6</sub>alkyloxy, cyano, nitro, polyhaloC<sub>1-6</sub>alkyl and polyhaloC<sub>1-6</sub>alkyloxy;

5 Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

15

The compounds of formula (II) can be prepared according to the methods described in the US patent applications with application number 60/143962 and 60/107792.

**20** (III) is an antiviral compound of formula



a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

**30**  $-a^1=a^2-a^3=a^4-$  represents a bivalent radical of formula

$$-\text{CH}=\text{CH}-\text{CH}=\text{CH}- \quad (\text{a-1});$$
$$-\text{N}=\text{CH}-\text{CH}=\text{CH}- \quad (\text{a-2});$$
$$-\text{N}=\text{CH}-\text{N}=\text{CH}- \quad (\text{a-3}) ;$$
$$-\text{N}=\text{CH}-\text{CH}=\text{N}- \quad (\text{a-4}) ;$$

**35**  $-\text{N}=\text{N}-\text{CH}=\text{CH}-$  (a-5);

$n$  is 0, 1, 2, 3 or 4; and in case  $-a^1=a^2-a^3=a^4-$  is  $(a-1)$ , then  $n$  may also be 5;

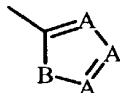
R<sup>1</sup> is hydrogen, aryl, formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxycarbonyl, C<sub>1-6</sub>alkyl substituted with formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxycarbonyl; and

40 C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxycarbonyl; and  
each R<sup>2</sup> independently is hydroxy, halo, C<sub>1-6</sub>alkyl optionally sub-  
stituted with cyano or -C(=O)R<sup>4</sup>, C<sub>3-7</sub>cycloalkyl, C<sub>2-6</sub>alkenyl  
optionally substituted with one or more halogen atoms or  
cyano, C<sub>2-6</sub>alkynyl optionally substituted with one or more  
45 halogen atoms or cyano, C<sub>1-6</sub>alkyloxy, C<sub>1-6</sub>alkyloxycarbonyl,  
carboxyl, cyano, nitro, amino, mono- or di(C<sub>1-6</sub>alkyl)amino,

## 6

polyhalomethyl, polyhalomethyloxy, polyhalomethylthio,  $-S(=O)_pR^4$ ,  $-NH-S(=O)_pR^4$ ,  $-C(=O)R^4$ ,  $-NHC(=O)H$ ,  $-C(=O)NHNH_2$ ,  $-NHC(=O)R^4$ ,  $-C(=NH)R^4$  or a radical of formula

5



(c)

wherein each A independently is N, CH or CR<sup>4</sup>;

B is NH, O, S or NR<sup>4</sup>;

10

$p$  is 1 or 2; and

R<sup>4</sup> is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C<sub>4-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>2-10</sub>alkynyl, C<sub>3-7</sub>cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

15

\* C<sub>3-7</sub>cycloalkyl,

\* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy,

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cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C<sub>1-6</sub>alkylcarbonyl,

\* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R<sup>2</sup>; or

25

L is  $-X-R^3$  wherein

R<sup>3</sup> is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with two, three, four or five substituents each independently selected from the substituents defined in R<sup>2</sup>; and

30

X is  $\text{-NR}^1\text{-}$ ,  $\text{-NH-NH-}$ ,  $\text{-N=N-}$ ,  $\text{-O-}$ ,  $\text{-C(=O)-}$ ,  $\text{-CHOH-}$ ,  $\text{-S-}$ ,  $\text{-S(=O)-}$  or  $\text{-S(=O)}_2\text{-}$ ;

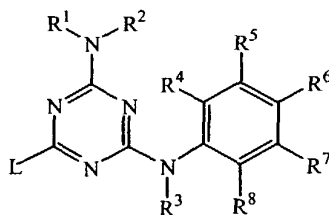
**35** aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>1-6</sub>alkyloxy, cyano, nitro, polyhaloC<sub>1-6</sub>alkyl and polyhaloC<sub>1-6</sub>alkyloxy.

40 The compounds of formula (III) can be prepared according to the methods described in the US patent application with application number 60/107799.

45

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(IV) is an antiviral compound of formula



(IV)

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the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen; hydroxy;

15

amino; C<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkylcarbonyl; C<sub>1-6</sub>alkyl-oxy-carbonyl; Ar<sup>1</sup>; mono- or di(C<sub>1-6</sub>alkyl)amino; mono- or di(C<sub>1-6</sub>alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C<sub>1-6</sub>alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonyl-amino, hydroxy, hydroxyC<sub>1-6</sub>alkyloxy, carboxyl, mono- or di(C<sub>1-6</sub>alkyl)amino, C<sub>1-6</sub>alkyloxycarbonyl and thienyl; or

20

R<sup>1</sup> and R<sup>2</sup> taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C<sub>1-6</sub>alkyl)aminoC<sub>1-4</sub>-alkylidene;

25

R<sup>3</sup> is hydrogen, Ar<sup>1</sup>, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy-carbonyl, C<sub>1-6</sub>alkyl substituted with C<sub>1-6</sub>alkyloxycarbonyl; and

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently selected from hydrogen, hydroxy, halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

L is C<sub>1-10</sub>alkyl; C<sub>3-10</sub>alkenyl; C<sub>3-10</sub>alkynyl; C<sub>3-7</sub>cycloalkyl; or

30

L is C<sub>1-10</sub>alkyl substituted with one or two substituents independently selected from C<sub>3-7</sub>cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C<sub>1-6</sub>alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C<sub>1-6</sub>alkylcarbonyl; and,

35

Ar<sup>1</sup> is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

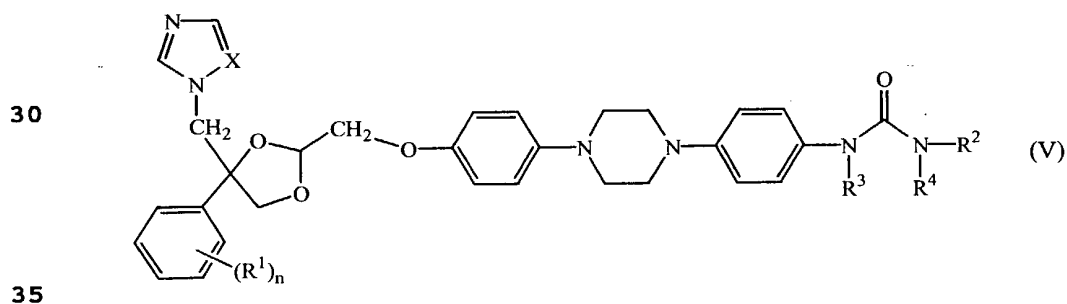
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	Co. No.	Alk	R <sup>1</sup> /R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	R <sup>7</sup>	R <sup>8</sup>
5	a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH <sub>3</sub>	H	H	H	H
	b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO <sub>2</sub>	H	H
	c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H
	d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO <sub>2</sub>	H	CH <sub>3</sub>	H	H
	e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH <sub>2</sub>	H	H
	f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF <sub>3</sub>	H	H	H
10	g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
	h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
	i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
	j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
	k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
15	l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
	m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
	n	Phenylmethyl	H/H	H	CH <sub>3</sub>	H	H	H	H
	o	Phenylmethyl	H/H	H	H	H	H	H	H

20 are not included.

The compounds of formula (IV) can be prepared according to the methods described in EP-A-0834507.

**25** (V) is an antifungal compound of formula



the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein  $n$  is zero, 1, 2 or 3;

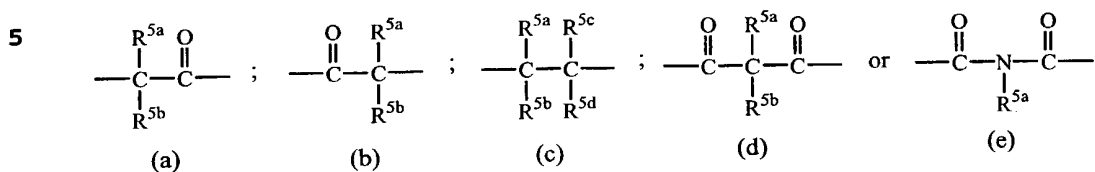
40 X is N or CH;

each R<sup>1</sup> independently is halo, nitro, cyano, amino, hydroxy, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxy or trifluoromethyl;

R<sup>2</sup> is hydrogen; C<sub>3-7</sub>alkenyl; C<sub>3-7</sub>alkynyl, aryl; C<sub>3-7</sub>cycloalkyl; C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl substituted with hydroxy, C<sub>1-4</sub>alkyloxy, C<sub>3-7</sub>cycloalkyl or aryl;

R<sup>3</sup> and R<sup>4</sup> each independently are hydrogen, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl or aryl; or

R<sup>3</sup> and R<sup>4</sup> taken together form a bivalent radical -R<sup>3</sup>-R<sup>4</sup>- of formula:



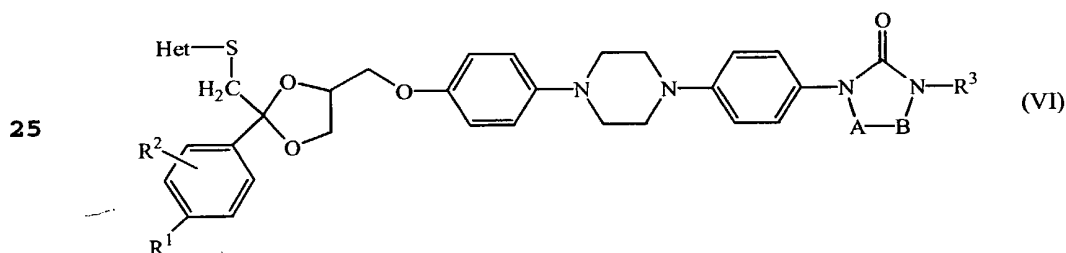
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wherein R<sup>5a</sup>, R<sup>5b</sup>, R<sup>5c</sup>, R<sup>5d</sup> each independently are hydrogen, C<sub>1-6</sub>alkyl or aryl; and aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxy or trifluoromethyl.

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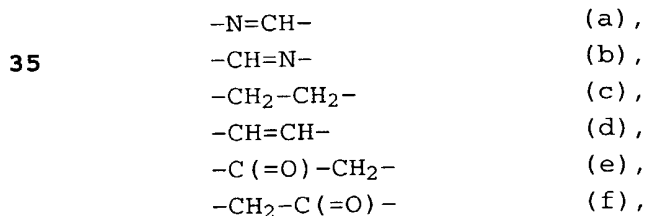
The compounds of formula (V) can be prepared according to the methods described in WO 99/02523.

20 (VI) is an apolipoprotein-B synthesis inhibitor of formula



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the N-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :



40 in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C<sub>1-6</sub>alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C<sub>1-6</sub>alkyl;

R<sup>1</sup> is hydrogen, C<sub>1-6</sub>alkyl or halo;

45 R<sup>2</sup> is hydrogen or halo;

R<sup>3</sup> is hydrogen; C<sub>1-8</sub>alkyl; C<sub>3-6</sub>cycloalkyl; or C<sub>1-8</sub>alkyl substituted with hydroxy, oxo, C<sub>3-6</sub>cycloalkyl or aryl;

## 10

- Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)amino or aryl; pyrimidine;
- 5 pyrimidine substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)-amino or aryl; tetrazole; tetrazole substituted with C<sub>1-6</sub>alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl,
- 10 hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)-
- 15 amino; oxadiazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or
- 20 di(C<sub>1-6</sub>alkyl)amino; thiazole; thiazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyl-oxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)amino;
- 25 aryl is phenyl or phenyl substituted with C<sub>1-6</sub>alkyl or halo.

The heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom.

- 30 The compounds of formula (VI) can be prepared according to the methods described in WO 96/13499.

- The particles comprise the compounds of formula (I) to (VI) as a solid dispersion in a polymeric matrix, wherein the poly-
- 35 meric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone. Furthermore, the invention concerns a process for manufacturing of such particles and pharmaceutical dosage forms comprising such particles.

- 40 The compounds of formula (I) to (VI) contained in the particles show poor bio-availability.

- In order to improve the dissolution characteristics the compounds are dispersed in a polymeric matrix, preferably by using a melt-
- 45 extrusion process.

## 11

EP-A 0 240 904 discloses a method for producing solid pharmaceutical forms by extrusion of polymer melts which contain active substances, using as polymers homo- or copolymers of N-vinylpyrrolidone.

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EP-B 0 580 860 discloses a method for producing solid dispersions of drug substances in a polymeric matrix using a twin screw extruder.

- 10 It is an object of the present invention to provide rate-controlled pharmaceutical forms containing the aforementioned compounds.

We have found that this object is achieved by the particles

- 15 defined at the outset.

Preferred compounds according to the invention are:

- 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;
- 20 4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile;
- 4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
- 4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-
- 25 amino]benzonitrile;
- 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-amino]benzonitrile;
- 4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;
- 30 4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
- 4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;
- 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-
- 35 pyrimidinyl]amino]benzonitrile;
- 4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile;
- 4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]-amino]benzonitrile;
- 40 4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;
- 1-[4-[4-[[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone;

45



- According to the present invention the term "rate-controlled" means that depending on the composition of the matrix the particles can show instant release of the active ingredient or modified release (sustained release).

The compounds according to the invention are homogeneously dispersed in a polymer matrix consisting of a homopolymer of N-vinylpyrrolidone or, preferably, a copolymer of N-vinylpyrrolidone. A preferred copolymer is a copolymer of N-vinylpyrrolidone and vinyl acetate, especially a copolymer obtained from 60% b.w. of NVP and 40% b.w. of vinylacetate.

- 20** The polymers show Fikentscher K values of from 17 to 90, preferably a K value of 30 (for the definition of the K value see "H. Fikentscher, Cellulose-Chemie" (1932), 58-64 and 71-74).

The polymeric matrix component is used in amounts of from 40 to 70, preferably of from 50 to 65% b.w. of the total weight of the particles.

In a preferred embodiment of the invention the polymeric matrix further comprises a surfactant, preferably a surfactant with a HLB-value of 10-18 (HLB: Hydrophilic Lipophilic Balance). Especially preferred surfactants are selected from the group consisting of low molecular weight polyoxyethylene polyoxypropylene block copolymers with a mean molecular weight of 1000 to 6000 g/mol, and hydrogenated castor oil which can be modified with polyethylene glycol.

The amounts of surfactants used lies in the range of up to 20% b.w., preferably 5 to 15% b.w., of the particles.

- 40 In another preferred embodiment the matrix further comprises an organic carboxylic acid in amounts of up to 5% b.w. of the particles.

In another preferred embodiment of the invention the polymeric matrix further comprises hydroxypropyl methyl cellulose in  
45 amounts of up to 25% b.w., preferably from 5 to 10% b.w..

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## 14

expected in view of the low solubility of the active ingredients in aqueous media.

## Examples

**5**

## General method

Powder mixes of the components were melt kneaded at 145°C for 5 min.. After cooling the solidified melts were ground and

10 sieved. The sieve fraction 0.5-1.5 mm was used for the dissolution tests.

The composition of the individual powder mixes is listed in Table 1.

## 15

Table 1

	Example No.	1	2	3	4	5	6
20	Active ingredient <sup>1)</sup>	30	30	30	30	30	40
	VP-VAC-copolymer <sup>2)</sup>	65	55	55	60	55	47,1
	Surfactant <sup>3)</sup>	5	15		5	5	4,3
	Citric acid				5		
	HPMC					10	8,6
	Surfactant <sup>4)</sup>			15			

25 <sup>1)</sup> 4-[[[4-[2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile

2) Kollidon® VA64, VP/VAC = 60/40, BASF Aktiengesellschaft

3) PEG-n-hydrogenated Castor oil

4) polyoxyethylene polyoxypropylene blockcopolymer, mean mol.

30 weight 4000 g/mol

The dissolution tests were carried out according to USP XXIII, paddle model, pH no change test, 0.1 M HCl, at 37°C, 100 rpm

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## 15

The results are listed in Table 2.

Table 2: Dissolution Rates of particles according to examples 1-6

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time [min]	Dissolution [%]				time [min]	Dissolution [%]	
	Ex. 1 (IR)	Ex. 2 (IR)	Ex. 3 (IR)	Ex. 4 (IR)		Ex. 5 (SR)	Ex. 6 (SR)
5	53	65	58	57	1		
10	73	86	88	82	2		
15	77	91	95	89	3		
20	81	91	96	93	4		
30	87	94	99	94	6		
15	60	92	93	96	8	96	95
120	93	94	97	95			
IR: Instant Release					SR: Sustained Release		

20 DSC-Measurements were performed with the formulations according to examples 1 to 6 in open pans (air) at temperatures of from 20 → 250°C, with a heating rate of 10°C per minute. There is no indication of crystalline drug substance in the solid dispersions.

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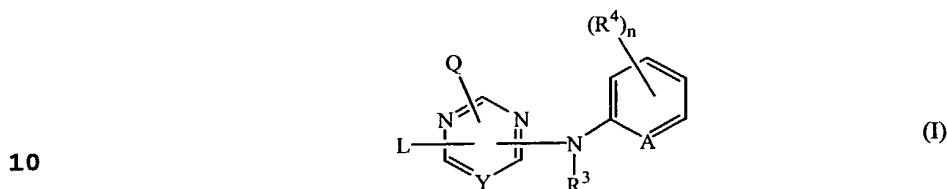
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## Claims

1. Rate-controlled release particles, comprising a compound of  
 5 formula I



a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

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Y is CR<sup>5</sup> or N;

A is CH, CR<sup>4</sup> or N;

n is 0, 1, 2, 3 or 4;

Q is -NR<sup>1</sup>R<sup>2</sup> or when Y is CR<sup>5</sup> then Q may also be hydrogen;

20

R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen, hydroxy, C<sub>1-12</sub>alkyl, C<sub>1-12</sub>alkyloxy, C<sub>1-12</sub>alkylcarbonyl, C<sub>1-12</sub>alkyloxycarbonyl, aryl, amino, mono- or di(C<sub>1-12</sub>alkyl)-amino, mono- or di(C<sub>1-12</sub>alkyl)aminocarbonyl wherein each of the aforementioned C<sub>1-12</sub>alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C<sub>1-6</sub>alkyloxy, hydroxy-C<sub>1-6</sub>alkyloxy, carboxyl, C<sub>1-6</sub>alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C<sub>1-6</sub>alkyl)amino, aryl and Het; or

25

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R<sup>1</sup> and R<sup>2</sup> taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C<sub>1-12</sub>alkyl)aminoC<sub>1-4</sub>-alkylidene;

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R<sup>3</sup> is hydrogen, aryl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxycarbonyl, C<sub>1-6</sub>alkyl substituted with C<sub>1-6</sub>alkyloxy-carbonyl; and

each R<sup>4</sup> independently is hydroxy, halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, or when Y is CR<sup>5</sup> then R<sup>4</sup> may also represent C<sub>1-6</sub>alkyl substituted with cyano or amino-carbonyl;

40

R<sup>5</sup> is hydrogen or C<sub>1-4</sub>alkyl;

L is -X<sup>1</sup>-R<sup>6</sup> or -X<sup>2</sup>-Alk-R<sup>7</sup> wherein

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R<sup>6</sup> and R<sup>7</sup> each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy,

## 17

5 C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl-  
oxycarbonyl, formyl, cyano, nitro, amino, and tri-  
fluoromethyl; or when Y is CR<sup>5</sup> then R<sup>6</sup> and R<sup>7</sup> may  
also be selected from phenyl substituted with one,  
two, three, four or five substituents each indepen-  
dently selected from aminocarbonyl, trihalomethyloxy  
and trihalomethyl; or when Y is N then R<sup>6</sup> and R<sup>7</sup> may  
also be selected from indanyl or indolyl, each of  
said indanyl or indolyl may be substituted with one,  
two, three, four or five substituents each  
10 independently selected from halo, hydroxy, C<sub>1-6</sub>alkyl,  
C<sub>1-6</sub>alkyloxy, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxycarbonyl,  
formyl, cyano, nitro, amino, and trifluoromethyl;  
X<sup>1</sup> and X<sup>2</sup> are each independently -NR<sup>3</sup>-, -NH-NH-, -N=N-,  
-O-, -S-, -S(=O)- or -S(=O)<sub>2</sub>-;  
15 Alk is C<sub>1-4</sub>alkanediyl; or  
when Y is CR<sup>5</sup> then L may also be selected from C<sub>1-10</sub>alkyl,  
C<sub>3-10</sub>alkenyl, C<sub>3-10</sub>alkynyl, C<sub>3-7</sub>cycloalkyl, or C<sub>1-10</sub>alkyl  
substituted with one or two substituents independently  
20 selected from C<sub>3-7</sub>cycloalkyl, indanyl, indolyl and  
phenyl, wherein said phenyl, indanyl and indolyl may be  
substituted with one, two, three, four or where possible  
five substituents each independently selected from halo,  
hydroxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl,  
25 C<sub>1-6</sub>alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl,  
trihalomethyloxy and C<sub>1-6</sub>alkylcarbonyl;  
aryl is phenyl or phenyl substituted with one, two, three,  
four or five substituents each independently selected  
from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, nitro and  
30 trifluoromethyl;  
Het is an aliphatic or aromatic heterocyclic radical;  
said aliphatic heterocyclic radical is selected from  
pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl,  
morpholinyl, tetrahydrofuranyl and tetrahydrothienyl  
35 wherein each of said aliphatic heterocyclic radical may  
optionally be substituted with an oxo group; and said  
aromatic heterocyclic radical is selected from pyrrolyl,  
furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and  
pyridazinyl wherein each of said aromatic heterocyclic  
40 radical may optionally be substituted with hydroxy,

or a compound of formula



**10**

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- 20

R<sup>1</sup> is hydrogen, aryl, formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxycarbonyl, C<sub>1-6</sub>alkyl substituted with formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxycarbonyl;

25

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wherein each A independently is N, CH or CR<sup>6</sup>;

$p$  is 1 or 2; and

polyhalomethyl;

L is C<sub>1-10</sub>alkyl, C<sub>2-10</sub>alkenyl, C<sub>2-10</sub>alkynyl, C<sub>3-7</sub>cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

\* C<sub>3-7</sub>cycloalkyl,

\* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C<sub>1-6</sub>alkyl-carbonyl,

\* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R<sup>2</sup>; or

L is  $-X-R^3$  wherein

R<sup>3</sup> is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R<sup>2</sup>; and

X is  $\text{-NR}^1\text{-}$ ,  $\text{-NH-NH-}$ ,  $\text{-N=N-}$ ,  $\text{-O-}$ ,  $\text{-C(=O)-}$ ,  $\text{-CHOH-}$ ,  $\text{-S-}$ ,  $\text{-S(=O)-}$  or  $\text{-S(=O)}_2\text{-}$ ;

Q represents hydrogen, C<sub>1-6</sub>alkyl, halo, polyhaloC<sub>1-6</sub>alkyl or -NR<sup>4</sup>R<sup>5</sup>; and

R<sup>4</sup> and R<sup>5</sup> are each independently selected from hydrogen, hydroxy, C<sub>1-12</sub>alkyl, C<sub>1-12</sub>alkyloxy, C<sub>1-12</sub>alkylcarbonyl, C<sub>1-12</sub>alkyloxycarbonyl, aryl, amino, mono- or di(C<sub>1-12</sub>alkyl)amino, mono- or di(C<sub>1-12</sub>alkyl)aminocarbonyl wherein each of the aforementioned C<sub>1-12</sub>alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C<sub>1-6</sub>alkyloxy, hydroxyC<sub>1-6</sub>alkyloxy, carboxyl, C<sub>1-6</sub>alkyloxycarbonyl, cyano, amino, imino, mono- or di(C<sub>1-6</sub>alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)<sub>p</sub>R<sup>6</sup>, -NH-S(=O)<sub>p</sub>R<sup>6</sup>, -C(=O)R<sup>6</sup>, -NHC(=O)H, -C(=O)NHNH<sub>2</sub>, -NHC(=O)R<sup>6</sup>, -C(=NH)R<sup>6</sup>, aryl and Het; or

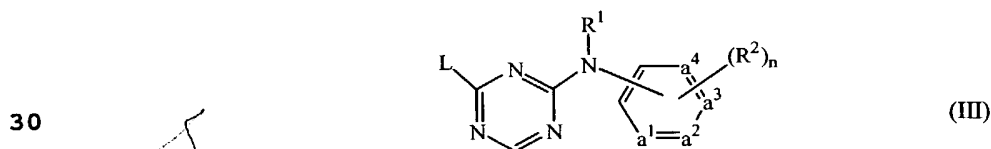
R<sup>4</sup> and R<sup>5</sup> taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C<sub>1-12</sub>alkyl)aminoC<sub>1-4</sub>-alkylidene;

45



## 20

- Y represents hydroxy, halo, C<sub>3-7</sub>cycloalkyl, C<sub>2-6</sub>alkenyl optionally substituted with one or more halogen atoms, C<sub>2-6</sub>alkynyl optionally substituted with one or more halogen atoms, C<sub>1-6</sub>alkyl substituted with cyano or  
 5 -C(=O)R<sup>6</sup>, C<sub>1-6</sub>alkyloxy, C<sub>1-6</sub>alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C<sub>1-6</sub>alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)<sub>p</sub>R<sup>6</sup>, -NH-S(=O)<sub>p</sub>R<sup>6</sup>, -C(=O)R<sup>6</sup>, -NHC(=O)H, -C(=O)NHNH<sub>2</sub>, -NHC(=O)R<sup>6</sup>, -C(=NH)R<sup>6</sup> or aryl;  
 10 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>1-6</sub>alkyloxy, cyano, nitro, polyhaloC<sub>1-6</sub>alkyl and polyhaloC<sub>1-6</sub>alkyloxy;  
 Het is an aliphatic or aromatic heterocyclic radical;  
 15 said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said  
 20 aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,  
 25 or a compound of formula



- a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof,  
 35 wherein

-a<sup>1</sup>=a<sup>2</sup>-a<sup>3</sup>=a<sup>4</sup>- represents a bivalent radical of formula

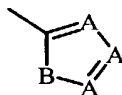
- CH=CH-CH=CH- (a-1);  
 -N=CH-CH=CH- (a-2);  
 -N=CH-N=CH- (a-3);  
 40 -N=CH-CH=N- (a-4);  
 -N=N-CH=CH- (a-5);

n is 0, 1, 2, 3 or 4; and in case -a<sup>1</sup>=a<sup>2</sup>-a<sup>3</sup>=a<sup>4</sup>- is (a-1), then n may also be 5;

- R<sup>1</sup> is hydrogen, aryl, formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxycarbonyl, C<sub>1-6</sub>alkyl substituted with formyl, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyloxycarbonyl; and  
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## 21

each  $R^2$  independently is hydroxy, halo,  $C_{1-6}$ alkyl optionally substituted with cyano or  $-C(=O)R^4$ ,  $C_{3-7}$ cycloalkyl,  $C_{2-6}$ alkenyl optionally substituted with one or more halogen atoms or cyano,  $C_{2-6}$ alkynyl optionally substituted with one or more halogen atoms or cyano,  $C_{1-6}$ alkyloxy,  $C_{1-6}$ alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di( $C_{1-6}$ alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio,  $-S(=O)_pR^4$ ,  $-NH-S(=O)_pR^4$ ,  $-C(=O)R^4$ ,  $-NHC(=O)H$ ,  $-C(=O)NHNH_2$ ,  $-NHC(=O)R^4$ ,  $-C(=NH)R^4$  or a radical of formula



(c)

wherein each A independently is N, CH or  $CR^4$ ;  
 B is NH, O, S or  $NR^4$ ;  
 p is 1 or 2; and  
 $R^4$  is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is  $C_{4-10}$ alkyl,  $C_{2-10}$ alkenyl,  $C_{2-10}$ alkynyl,  $C_{3-7}$ cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

- \*  $C_{3-7}$ cycloalkyl,
- \* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo,  $C_{1-6}$ alkyl, hydroxy,  $C_{1-6}$ alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and  $C_{1-6}$ alkyl-carbonyl,
- \* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in  $R^2$ ; or

L is  $-X-R^3$  wherein

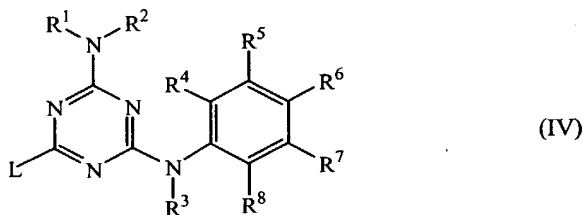
$R^3$  is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with two, three, four or five substituents each independently selected from the substituents defined in  $R^2$ ; and

X is  $-NR^1-$ ,  $-NH-NH-$ ,  $-N=N-$ ,  $-O-$ ,  $-C(=O)-$ ,  $-CHOH-$ ,  $-S-$ ,  $-S(=O)-$  or  $-S(=O)_2-$ ;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{1-6}$ alkyloxy, cyano, nitro, polyhalo $C_{1-6}$ alkyl and polyhalo $C_{1-6}$ alkyloxy,

22

or a compound of formula



10 the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen;

15 hydroxy; amino; C<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkylcarbonyl; C<sub>1-6</sub>alkyloxycarbonyl; Ar<sup>1</sup>; mono- or di(C<sub>1-6</sub>alkyl)amino; mono- or di(C<sub>1-6</sub>alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C<sub>1-6</sub>alkyl substituted with one or two substituents each independently selected from amino, imino, amino-carbonyl, aminocarbonylamino, hydroxy, hydroxyC<sub>1-6</sub>alkyl-oxy, carboxyl, mono- or di(C<sub>1-6</sub>alkyl)amino, C<sub>1-6</sub>alkyloxy-carbonyl and thienyl; or

20 R<sup>1</sup> and R<sup>2</sup> taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C<sub>1-6</sub>alkyl)aminoC<sub>1-4</sub>-alkylidene;

25 R<sup>3</sup> is hydrogen, Ar<sup>1</sup>, C<sub>1-6</sub>alkylcarbonyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy-carbonyl, C<sub>1-6</sub>alkyl substituted with C<sub>1-6</sub>alkyloxycarbonyl; and

30 R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently selected from hydrogen, hydroxy, halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

L is C<sub>1-10</sub>alkyl; C<sub>3-10</sub>alkenyl; C<sub>3-10</sub>alkynyl; C<sub>3-7</sub>cycloalkyl; or

35 L is C<sub>1-10</sub>alkyl substituted with one or two substituents independently selected from C<sub>3-7</sub>cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C<sub>1-6</sub>alkylcarbonyl; phenyl or 40 phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C<sub>1-6</sub>alkyl-carbonyl; and,

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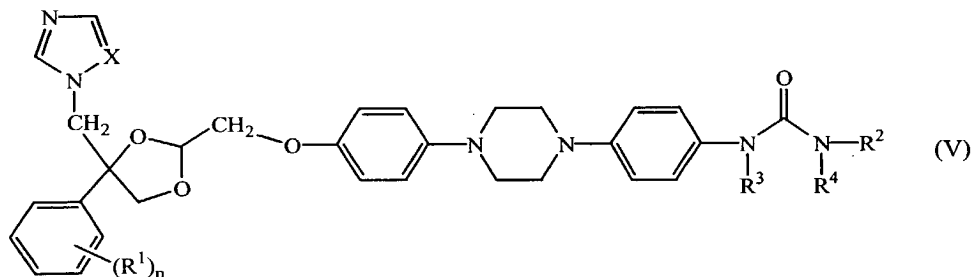
## 23

Ar<sup>1</sup> is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

Co. No.	Alk	R <sup>1</sup> /R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	R <sup>7</sup>	R <sup>8</sup>
a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH <sub>3</sub>	H	H	H	H
b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO <sub>2</sub>	H	H
c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H
d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO <sub>2</sub>	H	CH <sub>3</sub>	H	H
e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH <sub>2</sub>	H	H
f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF <sub>3</sub>	H	H	H
g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
n	Phenylmethyl	H/H	H	CH <sub>3</sub>	H	H	H	H
o	Phenylmethyl	H/H	H	H	H	H	H	H

are not included,

or a compound of formula



the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

*n* is zero, 1, 2 or 3;

*X* is N or CH;

each R<sup>1</sup> independently is halo, nitro, cyano, amino, hydroxy, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxy or trifluoromethyl;

R<sup>2</sup> is hydrogen; C<sub>3-7</sub>alkenyl; C<sub>3-7</sub>alkynyl, aryl; C<sub>3-7</sub>cycloalkyl; C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl substituted with hydroxy, C<sub>1-4</sub>alkyloxy, C<sub>3-7</sub>cycloalkyl or aryl;

R<sup>3</sup> and R<sup>4</sup> each independently are hydrogen, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl or aryl; or

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or a compound of formula

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R<sup>3</sup> is hydrogen; C<sub>1-8</sub>alkyl; C<sub>3-6</sub>cycloalkyl; or C<sub>1-8</sub>alkyl

substituted with hydroxy, oxo, C<sub>3-6</sub>cycloalkyl or aryl;

## 25

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)amino or aryl; pyrimidine; pyrimidine substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)-amino or aryl; tetrazole; tetrazole substituted with C<sub>1-6</sub>alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)-amino; oxadiazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)amino; thiazole; thiazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkyloxy, trihalomethyl, amino, mono- or di(C<sub>1-6</sub>alkyl)amino; aryl is phenyl or phenyl substituted with C<sub>1-6</sub>alkyl or halo, and the heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom,

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*Solution*  
as a solid ~~dispersion~~ in a polymeric matrix, wherein the polymeric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone.

- 35 2. Particles according to claim 1, wherein the copolymer of N-vinylpyrrolidone is a copolymer with vinyl acetate.
3. Particles according to claim 1 or 2, further comprising a surfactant.
- 40 4. Particles according to claim 3, wherein the surfactant is a PEG-n-hydrogenated castor oil.
- 45 5. Particles according to any of the claims 1 to 3, wherein the surfactant is a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

## 26

6. Particles according to any of the claims 1 to 3, further comprising citric acid in amounts of up to 5 % b.w.
7. Particles according to any of the claims 1 to 6, wherein the  
5 homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 40 to 70 % b.w. of the total weight of the dosage form.
8. Particles according to claim 7, wherein the homo- or copoly-  
10 mer of N-vinylpyrrolidone is used in amounts of from 50 to 65 % b.w..
9. Particles according to any of the claims 1 to 8, wherein the controlled release is an instant release of the drug.
- 15 10. Particles according to any of the claims 1 to 8, wherein the controlled release is a sustained release.
11. Particles according to claim 10, further comprising hydroxy-  
propyl methyl cellulose in amounts of from 5 to 10 % b.w..
- 20 12. Particles according to any of the claims 1 to 11, obtained by forming a homogeneous mixture of the components in the form of a melt, extruding said mixture and shaping of the extru-  
date.
- 25 13. Particles according to any of the claims 1 to 11, comprising a compound selected from the group consisting of
- 30 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile;
- 4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethyl-  
benzonitrile;
- 4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-  
pyrimidinyl]-amino]benzonitrile;
- 35 4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-  
amino]benzonitrile;
- 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-  
amino]benzonitrile;
- 4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-  
pyrimidinyl]amino]benzonitrile;
- 40 4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-  
pyrimidinyl]-  
amino]benzonitrile;
- 4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-  
pyrimidinyl]amino]benzonitrile;
- 45 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-  
pyrimidinyl]amino]benzonitrile;

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- 4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]-amino]benzonitrile;  
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile;  
5 4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;  
1-[4-[4-[4-[(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;  
10 (-)-[2*S*-[2*α*,4*α*(*S*<sup>\*</sup>)]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3*H*-1,2,4-triazol-3-one,  
a *N*-oxide, a pharmaceutically acceptable addition salt or a  
15 stereochemically isomeric form thereof.
14. Pharmaceutical dosage form, comprising particles according to any of the preceding claims.
- 20 15. Pharmaceutical dosage forms according to claim 13, further comprising one or more pharmaceutically acceptable excipients.

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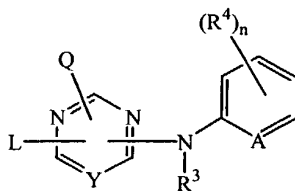
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## Abstract

Rate-controlled particles, comprising compounds of the formula



(I)

**15** as a solid dispersion.

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Dannstadt (DE). **ROSENBERG, Jörg** [DE/DE]; Bruch-  
strasse 29, 67158 Ellerstadt (DE). **BREITENBACH, Jörg**  
[DE/DE]; Hans-Sachs-Ring 95A, 68199 Mannheim (DE).

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(74) Agent: **GOLDSCHIED, Bettina**; BASF Aktiengesellschaft, 67056 Ludwigshafen (DE).

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(71) Applicant (*for all designated States except US*): **KNOLL AKTIENGESELLSCHAFT** [DE/DE]; 67061 Ludwigshafen (DE).

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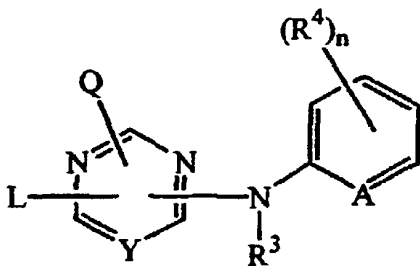
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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **HANTKE, Thomas** [DE/DE]; Landauerstrasse 5, 67067 Ludwigshafen (DE). **REHBOCK, Bettina** [DE/DE]; Wasgauring 28, 67125

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RATE-CONTROLLED PARTICLES



(I)

(57) Abstract: Rate-controlled particles, comprising compounds of formula (I) as a solid dispersion.

# Declaration, Power of Attorney

Page 1 of 3

We (I), the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Rate-controlled particles

the specification of which

☐ is attached hereto.

☒ was filed on May 19, 2002 as

Application Serial No. 10/088,400

and amended on

☒ was filed as PCT international application

Number PCT/EP00/09149

on 19 September 2000

and was amended under PCT Article 19

on (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
199 45 982.7	Germany	24 Sept 1999	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

We (I) hereby claim the benefit under Title 35, United States Codes, § 119(e) of any United States provisional application(s) listed below.

\_\_\_\_\_  
(Application Number)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Number)

\_\_\_\_\_  
(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.

Filing Date

Status (pending, patented,  
abandoned)

_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

2 -  
And we (I) hereby appoint Messrs. **HERBERT. B. KEIL**, Registration Number 18,967; and **RUSSEL E. WEINKAUF**, Registration Number 18,495; the address of both being Messrs. Keil & Weinkauff, 1101 Connecticut Ave., N.W., Washington, D.C. 20036 (telephone 202-659-0100), our attorneys, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to sign the drawings, to receive the patent, and to transact all business in the Patent Office connected therewith.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1-00

Thomas Hantke

Thomas Hantke  
Signature

Date: 1. Februar 2002

Residence:  
Richard-Wagner-Str. 33  
68165 Mannheim  
Germany  
Citizen of Germany

2-00

Bettina Rehbock

Bettina Rehbock  
Signature

Date: 1. Februar 2002

Residence:  
Wasgauring 28  
67125 Dannstadt  
Germany DEX  
Citizen of Germany

3-00

Jörg Rosenberg

Jörg Rosenberg  
Signature

Date: 1. Februar 2002

Residence:  
Bruchstrasse 29  
67158 Ellerstadt  
Germany DEX  
Citizen of Germany

4-00

Jörg Breitenbach

Jörg Breitenbach  
Signature:

Date: 1. Februar 2002

Residence:  
Hans-Sachs-Ring 95 A  
68199 Mannheim  
Germany DEX  
Citizen of Germany